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Biomonitoring Equivalents for interpretation of urinary iodine

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ABSTRACT

Iodine is an essential nutrient whose deficiency or excess exposure can cause adverse health effects. The primary sources of iodine exposure in the general population are iodized salt, dairy products, bread and sea food. Urinary iodine concentrations (UIC) have been measured by Canadian Health Measures Survey (CHMS) and US National Health and Nutrition Examination Survey (NHANES). The Institute of Medicine (IOM), the US Agency for Toxic Substances and Disease Registry (ATSDR) and World Health Organization (WHO) have established exposure guidance values for nutrition (IOM Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), WHO Recommended Nutrient Intake (RNI)) and toxicity (IOM Tolerable Upper Intake Level (UL); ATSDR Minimal Risk Level (MRL), WHO International Programme on Chemical Safety (IPCS) Tolerable Daily Intake (TDI)). Using a urinary excretion fraction of 0.9, Biomonitoring Equivalents (BE) for the EAR, RDA, UL and MRL were derived for adults (60, 100, 730 and 450 μg/L, respectively) and children (50, 80, 580 and 360 μg/L, respectively). The population median UIC values from NHANES and CHMS for adults (140–181, 122–126 μg/L, respectively) and children (232, 189 μg/L, respectively) were above the criteria for assessing iodine nutrition, indicating that US and Canadian populations are likely to have adequate population iodine nutrition. The median UIC from NHANES and CHMS do not exceed BE values derived from exposure guidance values for toxicity.

1. Introduction

Iodine is an essential trace element for human health. Iodine functions as a component of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) (Health Canada, 2012). Thyroid hormones are involved in regulating the body's metabolic processes and play a role in normal growth and development, particularly, in healthy brain development (CDC, 2012; WHO, 2007). According to the WHO, iodine deficiency is the single most important preventable cause of brain damage (WHO, 2007). Given the importance of adequate iodine intake for thyroid hormone synthesis and normal neurodevelopment, pregnant and lactating women and their offspring are the groups most vulnerable to iodine deficiency. Even a mild thyroid hormone insufficiency in pregnancy can produce measurable effects in very specific neurological functions (Ghirri et al., 2014; Zoeller and Rovet, 2004). The developmental timing of the thyroid hormone deficiency is critical to the type of neurological deficits that occur in the developing brain (Zoeller and Rovet, 2004). In humans, the thyroid hormone deficiency in the first and the second trimesters can have adverse effects in visual attention, visual processing, visuospatial skills and fine motor skills. If the deficiency occurs in late pregnancy, gross motor skills and memory can be affected (Zoeller and Rovet, 2004). Iodine deficiency in newborns can have predominant effects on verbal skills, language and motor function (Zoeller and Rovet, 2004). Iodine deficiency in newborns can also cause goiters and moderate to severe hypothyroidism (Ghirri et al., 2014; Katz et al., 2013).

Adverse effects associated with excess iodine intake are less obvious; the major epidemiological consequence of iodine excess is iodine-induced hyperthyroidism (WHO, 2007; 2004; Health Canada, 2012). Excess iodine intake has also been associated with thyroiditis, goiter, hypothyroidism, sensitivity reactions, thyroid papillary cancer, and acute toxic responses in some individuals (IOM, 2001).

Iodine is present in food and water primarily as iodide. Dietary sources of iodine include foods where iodine is added as a supplement (e.g., iodized salt, breads) as well as dairy products, and seafood (Health Canada, 2012). In North America, and much of the world, the addition of iodine to salt for table or household use is mandatory to prevent iodine deficiency (Health Canada, 2012). In households where food is prepared at home, iodized salt is the predominant source of iodine intake (Zimmermann and Andersson, 2012). However, most salt

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intake in Western diets (approximately 70%) is derived from processed food which is principally non-iodized salt (Caldwell et al., 2011). Murray et al. (2008) found that the primary contributors to dietary intake of iodine in the US population are dairy products and grains.

Due to the adverse outcomes associated with both iodine deficiency and excess iodine intake, assessing population iodine status is an imperative public health initiative. The use of median urinary iodine concentrations (UIC) from a population study is the most common measure used for examining iodine status in populations (WHO, 2007). The UIC is a well-accepted, cost-efficient and easily obtainable indicator for iodine status (WHO, 2007; 2004). UIC spot samples have been measured in large biomonitoring studies in North America including the National Health and Nutrition Examination Survey (NHANES) in the United States (US) and the Canadian Health Measures Survey (CHMS). Population iodine status is commonly evaluated by comparing the population median urinary iodine spot samples to threshold values derived by the World Health Organization (WHO) (WHO, 2007; Caldwell et al., 2011; Statistics Canada, 2013; Juan et al., 2016). The IOM and the US Agency for Toxic Substances and Disease Registry (ATSDR) have established exposure guidance values for iodine deficiency and excess intake for North Americans. These values are presented either as daily iodine intake (i.e., μg/d) or as a urinary creatinine adjusted value (i.e., μg/g creatinine) rather than UIC in μg/L, which is the biomarker recommended by the WHO for assessing iodine status (IOM, 2001; ATSDR, 2004; WHO, 2007). The purpose of this paper is to derive urine equivalent concentrations for the iodine exposure guidance values based on oral intake rates (ug/d) for North America using the Biomonitoring Equivalent approach.

The concept of Biomonitoring Equivalents (BEs) has been developed (Hays et al., 2007), and guidelines for the derivation and communication of these values have been prepared (Hays et al., 2008; LaKind et al., 2008). A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or Tolerable Daily Intake (TDI). Thus, the BE carries the same functional definition and intended use as the underlying guidance value (e.g., use for evaluating population risks the same as the RFD and TDI are intended). Existing chemical-specific pharmacokinetic data are used to estimate biomarker concentrations that are consistent with the Point of Departure (POD) used in the derivation of an exposure guidance value (such as the RfD or TDI), and with the exposure guidance value itself. BEs can be estimated for other types of exposure guidance values, including recommended intakes of nutritionally essential elements (e.g., selenium, Hays et al., 2014). BEs can be estimated using available human or animal pharmacokinetic data (Hays et al., 2008), and BEs have been derived for over 100 compounds to date (Aylward et al., 2013).

BE values are one of the tools available for the assessment of biomonitoring data (Angerer et al., 2011). These are intended to be used as screening tools to inform priority setting for risk assessment or risk management of exposures to chemical substances, in the same way that an RfD or TDI is used to evaluate estimated intakes of a chemical. For multiple chemicals, BE values have been used to evaluate CHMS and NHANES biomonitoring data across chemicals to examine relative levels of exposure in the context of risk assessment-derived exposure guidance values (St-Amand et al., 2014; Aylward et al., 2013). The derived BE values are only as robust as the underlying exposure guidance values and pharmacokinetic data used to derive them. BE values can leverage work conducted in existing risk assessments and place population-level biomonitoring data in a health risk context. While BE values are not intended to be used for assessing biomonitoring data from individuals or for diagnostic purposes, they are consistent with the usual application of the underlying risk assessment-derived exposure guidance values (Hays et al., 2008).

Table 1
Exposure guidance values for minimal nutritional needs of iodine from IOM (2001) and WHO (2007).

Life stage group	IOM (2001)			WHO, 2007	
	AI (μg/d)	EAR (μg/d)	RDA (μg/d)	Life stage group	RNI (μg/d)
Infants 0–6 mths	110	–	–		
Infants 7–12 mths	130	–	–		
Children 1–8 yrs		65	90	Children 0–5 yrs	90
Children 9–13 yrs		73	120	Children 6–12 yrs	120
Adults > 14 yrs		95	150	Adults > 12 yrs	150
Pregnancy		160	220	Pregnancy	250
Lactation		209	290	Lactation	250

AI - Adequate Intake, EAR - Estimated Average Requirement, RDA - Recommended Daily Allowance, RNI - Recommended Nutrient Intake.

2. Methods

2.1. Exposure guidance values

The IOM (2001) has derived Estimated Average Requirement (EAR) and Recommended Dietary Allowances (RDAs) to ensure nutritional adequacy of iodine intake. The EAR is the average daily nutrient intake level that is estimated to meet the requirement of half of the healthy individuals in a life-stage and sex group (IOM, 2001; Health Canada, 2010). The EAR is used to understand the average nutritional needs of a population. The RDA is derived from the EAR (by adding two standard deviations) and represents the average daily dietary intake level that is sufficient to meet the nutritional requirements of nearly all (97–98 percent) of the healthy individuals in the demographic group (IOM, 2001; Health Canada, 2010). The RDA is the target nutritional intake level for an individual (Health Canada, 2010). Similar to the RDA, the WHO has established a Recommended Nutrient Intake (RNI) for iodine to meet the nutrient requirements of almost all (97.5%) of healthy individuals in an age and sex-specific group (Table 1) (WHO, 2004). These values were established by estimating the average intake rates required to ensure nutritional sufficiency for normal thyroid function. The EAR, RDA and RNI values are delineated by age group and pregnancy status and are presented in Table 1.

Exposure guidance values have also been established to protect against adverse effects of excess iodine exposure. The IOM identified increased thyroid stimulating hormone (TSH), which can result in increased risk of clinical hypothyroidism, as the critical adverse effect for evaluation of the Tolerable Upper Intake Level (UL) (IOM, 2001). In two studies of controlled iodine administration in adults over a period of two weeks, intakes of approximately 1700–1800 μg/d resulted in increased levels of TSH (Paul et al. (1988) and Gardner et al., 1988, as reported in IOM, 2001). The IOM evaluation identified the lowest of these as the lowest observed adverse effect level (LOAEL). The evaluation concluded that uncertainty about extrapolation to a tolerable exposure level was low (due to the mild and reversible nature of the elevated TSH effects selected for the POD), and that an uncertainty factor of 1.5 was appropriate. This resulted in a UL of 1100 μg/d.

Both the ATSDR and the International Programme on Chemical Safety (IPCS) set exposure guidance values for iodine based on increases in thyroid stimulating hormone levels and increased prevalence of goiter in a high-exposure group of children compared to a lower-exposed group (Boyages et al., 1989; as cited in IPCS, 2009). The Minimal Risk Level (MRL) from ATSDR and the Tolerable Daily Intake (TDI) from the International Programme on Chemical Safety (IPCS) were derived based on the identification of a LOAEL of 1236 μg/g creatinine and a NOAEL of 428 μg/g creatinine iodine in urine in the lower exposure group (Table 2). Urine samples were collected from the participants involved in the study and iodine was quantified and reported as μg I/g creatinine. Based on the urinary excretion rates and average

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